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Amblyopia: literature review, definition, advances and treatment

Ambliopia: revisão da literatura, definição, avanços e tratamentos

Ambliopía: revisión de la literatura, definición, avances y terapia

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KEYWORDS:

Amblyopia; Strabismus; Anisometropia; Vision, Binocular.

ABSTRACT

Recent research on amblyopia has highlighted new concepts and a better understanding of this common vision-threatening clinical condition. The primary dysfunction within the amblyopic visual system occurs in the primary visual area or striate cortex (V1) area, and the amblyopic effect can be amplified in the higher areas of brain processing. Various simple and complex visual functions are affected in amblyopia, and significant clinical and functional differences exist in the patterns of visual loss among the clinically defined categories of amblyopia. Nevertheless, the substantial neural plasticity in the amblyopic brain beyond the "critical period" can potentially open the door for various treatments for amblyopia, even in teens and adults.

PALAVRAS-CHAVE:

Ambliopia; Estrabismo; Anisometropia; Visão Binocular.

RESUMO

Pesquisas recentes sobre a ambliopia enfatizaram novos conceitos e levaram a uma melhor compreensão dessa condição clínica comum que compromete a visão. A disfunção primária no sistema visual ambliópico ocorre na área visual primária ou córtex estriado (V1) e o efeito ambliópico pode ser amplificado nas áreas superiores do processamento cerebral. Várias funções visuais simples e complexas são afetadas na ambliopia e existem diferenças clínicas e funcionais significativas nos padrões de perda visual entre as categorias clinicamente definidas da ambliopia. Entretanto, a plasticidade neural significativa no cérebro ambliópico fora do "período crítico" tem o potencial de abrir as portas para vários tratamentos para a ambliopia, mesmo em adolescentes e adultos.

PALABRAS CLAVE:

Ambliopía; Estrabismo; Anisometropía; Visión Binocular.

RESUMEN

Investigaciones recientes sobre la ambliopía han puesto de relieve nuevos conceptos y así se ha alcanzado una mejor comprensión de esa condición clínica común que compromete la visión. La disfunción primaria en el sistema visual ambliópico ocurre en el área visual primaria también conocida como córtex estriado (V1) y el efecto ambliópico pode amplificarse en las áreas superiores del procesamiento cerebral. Se afectan varias funciones visuales sencillas y complejas en la ambliopía y hay distinciones clínicas e funcionales significativas en los estándares de pérdida visual entre las categorías clínicamente definidas de la ambliopía. Sin embargo, la plasticidad neural significativa en el cerebro ambliópico fuera del "período crítico" tiene el potencial de abrir puertas a varias terapias para el cuidado de la ambliopía, aun en adolescentes y adultos.

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INTRODUCTION

Definition

Amblyopia is clinically defined as the reduction of visual acuity (VA) in one or both eyes caused by abnormal binocular interaction during the critical period of visual development that cannot be attributed to any ocular or visual system abnormality or refractive error[1]. The American Academy of Ophthalmology considers amblyopia to be an interocular difference of two lines or more on the VA chart (without specifying any) or a VA worse than or equal to 20/30 with the best optical correction[2].

With a prevalence of 3%-6%, amblyopia is the second most common cause of low VA in children and adults and affects them economically and socially[3,4]. Individuals with amblyopia often have restricted career options and reduced quality of life owing to less social contact, cosmetic distress (if associated with strabismus), low self-esteem, visual disorientation, and fear of losing vision in the other eye[5-8].

Physiopathology

Classically, amblyopia is defined as a decrease in VA, decrease in contrast sensitivity of high spatial frequencies, and binocular vision deficit; however, it can also affect the development of a broad range of neural, sensory, oculomotor, and perceptual functions of vision[9-11].

Notably, various visual functions are underdeveloped at birth. The complete development of these functions during the critical period of visual development in infancy depend on the following three fundamental conditions: adequate stimuli received from each eye, ocular parallelism (corresponding images), and integrity of the visual pathways.

However, disturbances in the input of stimuli received by the visual cortex during this plastic and unstable stage of visual development prevent the proper use of input from the affected eye, thereby resulting in amblyopia. The effects of the visual system are closely related to the time of the advent of visual disturbance along with its intensity, type, and duration.

When the visual stimulus disorder is precocious, severe, unidentified, and not reversed during the first months or years of life, it can lead to profound structural modification of visual neuronal circuit, causing definitive morphological changes in cortical structures of lateral geniculate nucleus and the visual cortex, leading to definite alterations in the final visual function[12].

Nevertheless, when the visual stimulus disorder develops and is less intense, the normal anatomy of the visual system is maintained, albeit with the possibility of active inhibition from neurons of the normal eye on neurons of the affected eye, which also results in functional amblyopia. In such instances, the neurological mechanism inhibits the image formed in the affected eye to facilitate undisturbed processing of the normal eye[13].

Because amblyopia is a visual development disorder, early diagnosis of ocular changes associated with amblyopia is crucial for an excellent visual prognosis by allowing treatment at a stage where the visual neurological pathways are still amenable to stimulation, recovery, and reversal of the cortical damage.

The main ocular alterations that predispose to amblyopia are as follows: deprivation of visual stimuli (pupil occlusion by ptosis, opacities of optical media, nystagmus, and several others), alteration of sharpness of visual stimuli owing to refractive changes (high ametropia or anisometropia), and non-corresponding images received by each eye (strabismus).

TYPES OF AMBLYOPIA

Deprivation amblyopia

Deprivation happens when eye diseases prevent the light stimulus from reaching the retina, thereby preventing the normal visual process and can cause amblyopia if it occurs during the critical period of visual development. The deprivation is primarily caused by diseases, such as congenital cataract, blepharoptosis, and persistent fetal vasculature.

Seminal studies by Hubel and Wiesel had demonstrated that suturing the eyelid of cats deprived the eye of visual stimuli and led to several anatomical and functional changes in the cortical visual pathways. Moreover, these changes were observed to be more drastic if the deprivation occurred earlier in life and was more intense and prolonged[14-21].

Similarly, several authors have proven that deprivation adversely affects children's vision variously, and the period and severity of deprivation can result in various deficits in the final visual function[22,23].

The ideal period to treat the causes of deprivation in humans is within the sixth month of life because the effectiveness of treatment and ability to achieve normal results decrease rapidly after that period[24]. Notably, the severity of deprivation makes a difference in these first 6 months. For instance, dense bilateral cataracts not treated by 3 months of age will

undoubtedly lead to the development of nystagmus, which will severely limit the VA permanently[25].

Deprivation amblyopia causes profound anatomical changes in the visual circuitry and has the greatest influence on the VA and all other visual functions. Therefore, its treatment is challenging, with less successful results compared with other forms of amblyopia[4,24,26].

Anisometropic amblyopia

Anisometropia is the difference of at least 1 diopter in the states of refraction between the two eyes[27]. The prevalence of anisometropic amblyopia is about 4.7% in children and can be myopic, astigmatic, or hypermetropic.

Notably, hypermetropic anisometropia is the most likely cause of amblyopia because the retina of the more ametropic eye never receives a clear and defined image. Typically, the fovea of the normal eye is focused, and there will be no stimulus of accommodative effort to adjust the focus of the more hyperopic eye. In myopic anisometropia, the more ametropic eye can be used for near vision, preventing the same levels of amblyopia experienced with hyperopia[1,28,29].

Anisometropia may be considered a moderate form of deprivation of visual stimulus because the more ametropic eye is deprived of receiving a good-quality stimulus in the retina. Anatomical and functional changes owing to deprivation can, therefore, be expected in anisometropic amblyopia[30,31].

The severity of amblyopia is not directly related to the magnitude of the refractive degree but to the amount of anisometropia between the two eyes, thereby suggesting that mechanisms other than an optical blur, especially abnormal binocular interactions, are involved in the risk of amblyopia[31,32].

Despite differences in the inputs received from each eye, in anisometropia, both eyes receive congruent images, and unlike strabismus, there is no stimulation of non-corresponding retinal areas[33,34]. Therefore, pure anisometropic amblyopia classically leads to substantial VA deficits compatible with the loss of contrast sensitivity of all spatial frequencies; however, with relative sparing of binocular vision[10,35,36].

Anisometropic amblyopia has the best prognosis among all amblyopia types, with sometimes an unexpected recovery of VA with only the use of adequate correction and even with later treatments[37]. Studies have shown that the presence of preserved or subnormal binocular function is a crucial factor for the recovery of the visual system, although these researches have shown that besides the conventional monocular occlusive treatment, other forms of balanced binocular (dichoptic) treatment are ideal for restoring the normal visual functions[38-40].

Strabismic amblyopia

Strabismus is the deviation of one eye with loss of eye parallelism. Consequently, the eyes do not receive corresponding images, forcing the visual system to adapt to this change[1].

When the visual system is completely formed (adults), the perception of non-corresponding images by two eyes leads to double vision but when the visual system is in its critical period of development (childhood), the brain is still capable of using mechanisms to avoid diplopia or rivalry by inhibiting the activation of the retinocortical pathways originating from the fovea of the deviating eye. Even though this adaptive mechanism prevents diplopia, it causes a restructuring of the visual cortical circuits in the visual cortex, thereby causing amblyopia.

Tychsen et al. have demonstrated several visual function alterations in monkeys with strabismus and loss of V1 binocular connections[17-19,41]. Notably, the severity of motor ocular changes and the loss of V1 binocular connections increased as a function of the decorrelation duration, in that the animals treated until 3 weeks of decorrelation recovered these functions.

Strabismus causes changes in the cortical spatial information pathways or a loss of connectivity to it, altering the spatial summation and side inhibitions of the stimuli received, which consequently prevents the integration of contours and shapes. The spatial vision is, therefore, distorted, which interferes with numerous discriminatory visual tasks, such as VA, Vernier VA (alignment accuracy), and crowding[42-47].

In strabismus, there is no binocular facilitation for any form of stimulus, and the suppression is constant and strong[34]. Suppression is also seen in the fovea of the normal eye when the amblyopic eye is fixing, thereby indicating that the lost VA is not solely related to suppression. Thus, it is suppression that leads to amblyopia in an individual who has strabismus and not vice versa because the inactivity of the system may interfere with the process of synaptic development[48].

In strabismus, the different stimuli received by the eyes prevent normal image fusion compromising binocular vision, summation, and the ability to discriminate disparity and depth of vision with altered stereoscopic VA (stereopsis) and even postural stability[6,49-56].

Mixed amblyopia

Mixed amblyopia occurs when two amblyogenic factors are involved, with the most common being the combination of anisometropic and strabismic amblyopia is common, primarily observed in partially accommodative esotropia, microtropia, and monofixation syndrome[1,36].

Clinically, mixed amblyopia is more severe with several visual function deficits, besides an exacerbation of VA loss, contrast sensitivity, and typically extinction of stereopsis. However, the magnitude of the effect on each visual function depends on the simultaneous onset or on the different times at which each ocular change occurs[6].

OTHER CORTICAL AREAS AND COMPLEX FUNCTIONS AFFECTED BY AMBLYOPIA

Amblyopia is, therefore, a neural disorder resulting from abnormal brain stimulation during the critical period of visual development. Several studies have indicated that the primary cortical area affected by amblyopia is V1. Amblyopes have decreased binocular neurons and neurons responsible for the amblyopic eye in V1 besides having active binocular suppression[14,41,57-63].

Recent research has shown that despite the well-known visual processing deficits, amblyopic patients present with alterations in visual processing of high-order cortical functions[64], such as a deficiency in movement integration[65], perception and processing of shape and global contour[66-69], altered perception of alignment (Vernier acuity), and symmetry[70,71]. In addition, deficits have been observed in tasks involving high-order attention components[45,72-79], such as enumeration of objects, prolonged attentional blinking, the “crowding” phenomenon, reading process, and visual decision-making. Recent evidence shows that the perceptual influence of amblyopia extends beyond vision to multisensory processing[80], with abnormalities evident in the audiovisual speech perception[81-83], spatial audiovisual localization[84], and temporal judgment tasks[85].

Furthermore, these high-order deficits are observed in the fellow eye[45,86-88,89,90] and during binocular vision[75,80,91,92].

The common element in all these affected sensory-motor tasks is that they are not limited to acuity and require both local and global cortical processing[67,93] and involve extraction and segregation of a background noise signal[94-96], clearly implicating high-order visual processes[35,97-99].

Studies have used functional magnetic resonance imaging to confirm the different effects on the visual cortex related to different types of amblyopia. Recent findings have suggested more profound disorganization of the cortical arrangement in patients with strabismic amblyopia, wherein the interhemispheric asymmetry for parvo- and magnocellular input processing was lost, whereas normal cortical asymmetry was present in those with anisometropic amblyopia[100-102].

Recent research has shown that amblyopia causes abnormality in multisensory brain processing that persists even in binocular condition. Experiments of Richards et al. have demonstrated alterations in the temporal, spatial, and speech audiovisual perception in amblyopic subjects, indicating that amblyopia causes not only unisensory visual impairment but also alterations in multisensorial brain processing[80,84,85].

DIAGNOSIS

Despite the variations in visual function deficits, amblyopia is still diagnosed by measuring the VA on an eye chart by using optotype-based recognition.

Preverbal children who cannot complete this task are diagnosed using behavioral methods, such as the fixation preference, which is performed by observing the vigor with which the child objects to the occlusion of one eye relative to the other. Grading schemes can be used to quantitatively measure the fixation preference[103], besides doing the grating acuity test by using the Teller acuity cards[104]. Recognition VA testing based on optotypes (letters, numbers, or symbols) must be done as soon as the child can perform this task reliably[105].

Because amblyopia is a common and preventable visual deficit, there is immense concern regarding its early diagnosis and in determining more effective treatments for the condition. The American Academy of Pediatrics recommends pediatricians or family care practitioners to screen the child for amblyopia as part of the regular well-child visit, including the use of instrument-based vision screening techniques for preverbal children[106].

Randomized longitudinal studies have shown that screening improves vision outcomes and decreases the prevalence of amblyopia by as much as 60%[107]. Moreover, novel technologies, such as instrument-based devices (vision screeners), enable primary care providers to diagnose amblyopia in the early stages and refer children for specialized ophthalmologic care[108-110]. Early detection can facilitate timely treatment and result in better outcomes for children[111].

TREATMENT

The gold standard treatment for amblyopia is patching the better eye to force the brain to use the weaker eye. Depriving the fellow or fixating eye of vision forces the amblyopic eye to strike suppression and use the visual cortex corresponding to the eye to recover connections for better vision. Alternatives to patching are optical penalization with atropine eye drops, filters to blur the better eye, optical defocus using glasses or contact lenses, and dichoptic video games.

In the last 20 years, groups such as PEDIG (Pediatric Eye Disease Investigator Group)[112,113] and MOTAS (Monitored Occlusion Treatment of Amblyopia Study)[114] have conducted randomized clinical trials to address the primary issues of occlusive treatment and define the optimal treatment protocols.

The PEDIG studies have published 17 Amblyopia Treatment Studies (ATS), which have evaluated the amblyopic treatment for children aged 3 to 17 years, and the significant results to date are as follows:

1. Optical correction alone is successful in improving the amblyopia in nearly one-third of patients[37,115].
2. Patching is an effective treatment for amblyopia[116].
3. The ideal number of hours of patching was evaluated. Children aged 3 to 7 years with moderate amblyopia were randomized to 2 hours of patching per day compared with 6 hours of patching daily. Although the 6-hour occlusion group had faster improvement, at the end of 4 months of treatment both groups achieved similar VA (20/30 VA or at least an improvement of three lines from baseline), with no statistically significant intergroup difference[117]. Another ATS evaluated severe amblyopia (20/100 to 20/400) and compared between groups using 6 hours of patching and full-time patching. At the end of the treatment period, both groups had favorable outcomes with an average improvement in VA of 4.8 lines (6 hours) and 4.7 lines (full time) with no statistically significant intergroup difference[118]. Nevertheless, higher hours of patching were associated with worse compliance, with only 6% of patients complying with the prescribed time[119]. These studies provide useful information regarding the effect of the prescribed number of hours on the VA. However, it is imperative to follow prudence by customizing patching treatment for each patient based on the time of onset of amblyopia and the different etiologies[3].
4. Atropine for penalization proved to be as effective as occlusion. Although the occlusion group had a quicker improvement in the VA, at the end of 6 months of treatment both the two groups had an equal improvement in the VA, which was maintained over a long term of follow-up (up to 15 years). In addition to daily atropine, the use of atropine once a week showed improvement in the VA and better compliance among patients[120].
5. Treatment of amblyopia is most effective under 7 years of age. Children up to 13 years of age showed significant improvement in vision with patching, albeit with a slower rate of response to treatment, a higher dose of patching, and incomplete recovery[121].
6. Amblyopia treatment, with both occlusion and atropine, had an identical high rate of recurrence (approximately 25%) at the end of treatment. Notably, this rate was four times higher in children who did not have a gradual taper of their treatment for at least 5 weeks after the resolution of amblyopia. The other factors linked with the high recurrence rates were better VA at the end of treatment, a greater number of lines of improvement, and previous history of recurrence[122,123].
7. Children who performed near work for a better part of their patching time had more improvement than children who did no near work as part of the patching regimen[124,125].

   Nonetheless, the results of this series of studies should be analyzed with caution because no individual analysis is available for each type of amblyopia, dysfunctions of earlier or later onset, or factors that cause diverse dysfunctions in visual functions with different prognosis.

   Therefore, more than proposing new regimens of patching treatment hours, the study data help us to understand the effect of the prescribed occlusion hours. Thus, the conventional treatment regimens remain valid, and each case must be analyzed and treated individually.

NEW PERSPECTIVES IN AMBLYOPIA

Over the years, the study of amblyopia has enabled to understand the brain function better. The study of Hubel and Wiesel on animal models demonstrated anatomical and functional alterations in the primary visual cortex owing to amblyopia. However, since then, much has been discovered regarding the effect of amblyopia on the visual system and the significance of the critical period of cerebral plasticity on the effectiveness of treatment. Nevertheless, these research have caused two major shifts in the para-

digm concerning amblyopia, namely the perspectives that successful treatment of amblyopia is possible beyond the critical period and amblyopia is more of a binocular disease than a monocular one[126].

Treatment of amblyopia outside the critical period

It is well-known that the young brain is more plastic than an adult brain, but also known is the fact that the adult brain is still capable of learning and recovering after an injury. Thus, there is plasticity at the synaptic level, cellular level, and the level of cortical representation. One interpretation of this context is that the critical period ends with an increased threshold for plasticity rather than complete closure; therefore, it is necessary to find stimuli and ways to stimulate the specific plasticity of the adult brain[11,126].

Intracortical inhibitory circuitry was discovered to be a key factor in defining the limits of cortical plasticity. A brief reduction of GABAergic inhibition in the brains of rats was shown to be able to reopen a window of plasticity in the visual system well after the normal closure of the critical period[127]. Therefore, several intrinsic and extrinsic modes of augmentation of plasticity have been employed to facilitate amblyopia therapy beyond the critical period of development.

Intrinsic augmentation can be achieved by manipulating the neurotransmitter systems that regulate synaptic plasticity environmentally or behaviorally. One can stimulate this system through environmental enrichment (exercise and visual enrichment), prolonged dark exposure, caloric restriction, and with new or challenging visual tasks (perceptual learning)[11,128-132].

Extrinsic augmentation involves exogenous manipulation of the endogenous neuromodulatory system. One of these methods is pharmacological, and the most commonly used drug for this purpose is levodopa. However, a randomized, placebo-controlled clinical trial conducted by PEDIG showed that the improvement in VA with levodopa did not have a statistically significant difference compared to the placebo, and the improvement in vision in the levodopa group was not sustained during follow-up after stopping the medication[133].

Notwithstanding, another possibility would be to use medications that alter the expression of genes to remove the molecular "brakes" on cortical plasticity[134-137].

The neuromodulatory system can also be accessed through direct and noninvasive activation by using subthreshold electric current or transcranial magnetic stimulation. Transcranial direct current stimulation and transcranial magnetic stimulation have been employed to facilitate plasticity in stroke patients and patients with amblyopia. Both techniques have shown improved contrast sensitivity in amblyopic patients and facilitated stereopsis, albeit with clinically insignificant results[138].

Amblyopia as a binocular disease

Amblyopia typically affects the VA in one eye and was always considered a monocular disease. Accordingly, the primary treatment is often the occlusion of the fellow eye to improve the monocular function of the amblyopic eye. However, several studies have demonstrated that the deficit in amblyopia extends beyond monocular VA impairment and into higher-order functions, such as binocular vision, fixation instability, and visuomotor activities owing to abnormal interocular interactions[10,139,140]. The common element in these additional deficits in amblyopia is that they are not acuity-limited tasks; instead, they require integration of information over relatively large regions of space and time and involve extracting a signal from noise[62]. These deficits are not corrected by monocular treatment and remain even when the VA recovers after patching.

Based on these findings, it has been argued that amblyopia is intrinsically a binocular problem and that the suppression should be addressed first during the treatment of amblyopia, rather than hoping to restore binocular vision after monocular acuity improvement with occlusion therapy. Based on this suggestion, new binocular treatments have been proposed. Hess, Mansouri, and Thompson proposed a treatment based on strengthening binocular combination through a gradual reduction in suppression[38,141,142]. Using this binocular approach, they demonstrated that individuals with strabismic amblyopia could combine the information normally between their eyes when the suppression was reduced by presenting stimuli of different contrasts to each eye through dichoptic viewing[6]. Based on these findings, these authors proposed a new type of treatment for amblyopia, commonly called the dichoptic treatment. The treatment strategy aims to stimulate the two eyes simultaneously, thereby promoting the possibility of improvement of monocular VA of the amblyopic eye besides combating the suppression and working to normalize binocular interactions for recovery of binocular vision.

This concept has been applied to passive and active forms of training for amblyopia. Passive training modalities include watching movies under dichoptic viewing conditions[39]. Active training applies perceptual learning using hand-held tablets, which when combined with red-green glasses, presents video games that require a binocular function to complete the game's objective[40,143-145]. Both active and passive strategies of dichoptic treatment have shown favorable results with the improvement of the VA and in several cases resulted in normalization or recovery of binocular vision, including in adult individuals.

Given these promising results, PEDIG conducted a large, randomized, controlled trial on patients aged 5 to 13 years to compare between playing 1 hour of falling blocks game daily and patching for 2 hours daily over 16 weeks. The study revealed a poor adherence to the game regimen prescribed and the improvement in the VA, for this particular game, was not as good as that with 2 hours of prescribed daily patching[146]. Similar results were observed in another well-designed, multi-center randomized clinical trial (BRAVO study)[147].

Albeit these disappointing results, the authors encourage new research using more engaging gameplay to reduce noncompliance owing to the nature of the game, like the falling blocks game, which is not appealing to children. Nevertheless, new protocols with different and more engaging games, such as action-oriented adventure games, first-person shooter games, virtual reality, and 3-dimensional gaming platforms are being analyzed for this purpose[148-150].

Although the dichoptic treatment did not show substantial improvement in the VA and stereopsis, all protocols showed improved contrast processing during the games, which suggest better binocular interaction and decreased suppression. Therefore, it is imperative to evaluate the improvement in other visual functions that are altered in amblyopia, which depend directly on the normal binocular interaction, such as Vernier acuity, contrast sensitivity of different levels of complexity, global movement tasks, fixation stability, and even quality of life through questionnaires to assess the subjective perception of each individual regarding their vision changes.

A more meticulous, global study of individuals with amblyopia can provide explanations regarding the high variability of response to treatment in these individuals. Moreover, it can help us define, understand, and categorize amblyopia better, thereby helping to prepare a more customized treatment for each patient[151].

CONCLUSION

Recent research on amblyopia has introduced new concepts and provided a better understanding regarding this common vision-threatening clinical condition. Therefore, we now know that the primary dysfunction within the amblyopic visual system first occurs in V1 area and the effect caused by amblyopia can be amplified in the higher areas of processing. In addition, we are aware of the significant clinical and functional differences in the patterns of visual loss among the clinically defined categories of amblyopia. Most importantly, we comprehend that substantial neural plasticity exists in the amblyopic brain beyond the "critical period," which can potentially facilitate the use of different treatments of amblyopia, even during teens and adulthood.

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